University of California
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March 31, 2014

Dear Mr. Khalil,

We extend our most sincere thanks for your participation in our research programs. Postmortem studies are extremely important to the advancement of research on nervous system disorders and your contribution to research is invaluable.

Enclosed is the final neuropathology report for your wife. The scientific procedures and analyses for determining the postmortem diagnosis required many months to complete and were performed by a team of dedicated physicians and researchers in a multidisciplinary manner. Thank you for your patience as we finalized the report.

This is a complex and technical document that often requires interpretive discussion with a clinician. I hope this report and a discussion with a Memory and Aging Center neurologist will allow you and your family a greater understanding of your wife's disease. I will be in contact with you regarding a few times that Dr. Bruce Miller is available to go over the results with you. If there are any other family members that would like to be part of the conversation, please let me know, and I will arrange for a conference call to be set up.

It has been a privilege to work with your family, and we remain available to you at any time.

Warmest regards,

[redacted]

Kelly Hitchner
Administrative Manager, Autopsy Program
[redacted]

UCSF Alzheimer's Disease Research Center
Neuropathological Assessment

March 21, 2014

Patient name: Khalil, Karen
P #: P2471

Final Neuropathological Diagnoses

Primary diagnosis: Frontotemporal lobar degeneration with TDP-43 immunoreactive inclusions (FTLD-TDP), Type C, and primary lateral sclerosis[1]

Incidental diagnosis #1: Arteriolosclerosis, moderate overall severity
Incidental diagnosis #2: Alzheimer's disease neuropathological change (ADNC)[2]

- a. Low ADNC, NIA-AA Criteria (A1, B0, C0)
- b. Thal Amyloid Plaque Phase 1
- c. Braak Neurofibrillary Degeneration Stage 0
- d. CERAD Neuritic Plaque Score absent
- e. NIA-Reagan Criteria not met

Clinical History

This 65-year-old woman's illness began at age 49, with first symptoms relating to emotional distance from family, irritability, and anxiety, progressing to profound semantic deficits with striking preservation of visuospatial skills. The clinical syndromic diagnosis was the right temporal variant of semantic dementia (now referred to as semantic variant primary progressive aphasia), thought most likely due to underlying frontotemporal lobar degeneration (FTLD) pathology. The family history was not contributory. Full details of the clinical history can be found in the patient's research records.

Autopsy Details

Time of death:	6/9/2013
Time of procurement:	6/9/2013 6:15:00 PM
Time of fixation:	6/9/2013 6:35:00 PM
Post-mortem interval:	18.6 hours
Materials received:	Entire right cerebral hemisphere, left cerebellar hemisphere, and whole brainstem and spinal cord, fixed in 10% neutral buffered formalin
Fresh brain weight:	800 grams

Gross Observations

Dura:	NA
Superior sagittal sinus thrombus:	NA
Leptomeninges:	NA
Atherosclerosis:	Mild
Lacunar infarcts:	Absent
Territorial infarcts:	Absent
Intracranial hemorrhages:	Absent
Cortical laminar necrosis:	Absent
Ventricular enlargement:	Moderate
Substantia nigra pigment loss:	Absent
Spinal cord, ventral rootlets:	Normal
Other gross findings:	Moderate to severe atrophy involving anterior temporal, anterior insular, and medial/orbital/lateral frontal lobes, as well as milder amygdala and hippocampus involvement

Microscopic Findings

Hematoxylin & Eosin (H&E) stain

Cortical microvacuolation was examined across multiple regions to establish a regional pattern of pathology. Gliosis was examined in cortex and deep structures. Marked neuronal loss (> 50%) was graded when present.

Region	Subregion	Side	Microvacuolation	Astrogliosis	Neuron Loss
Frontal	Frontal pole	R	+	+	
	Anterior orbital gyrus	R	+	+	
	Anterior cingulate cortex	R	++	++	
	Middle frontal gyrus	R	+	+	
	Inferior frontal gyrus, pars opercularis	R	++	++	
	Subgenual cingulate cortex	R	Not identified	Not identified	
	Precentral gyrus	R	++	+++	
	Superior frontal sulcus	R	+	++	
Insula	Middle insula	R	++	+++	+
Temporal	Entorhinal cortex	R	+++	+++	+++
	Inferior temporal gyrus	R	+++	+++	+++
	Superior/middle temporal gyrus	R	+	++	
Parietal	Postcentral gyrus	R	+	+	
	Posterior cingulate cortex	R	+	+	
	Angular Gyrus	R	+	+	
Occipital	Striate cortex	R	0	0	
Limbic	Amygdala	R		++	
	Dentate gyrus	R		0	
	CA3-4	R		0	
	CA2	R		0	
	CA1/Subiculum	R		0	
Subcortical	Ventral striatum	R		+++	++
	Putamen	R		++	
	Globus Pallidus	R		0	
	Subthalamic nucleus	R		0	
	Thalamus	R		++	
	Claustrum	R		+	
Cerebellum	Dentate nucleus	L		0	
	Folia	L		0	
Midbrain	Substantia Nigra	B		0	
	Tectum	B		0	
	Periaqueductal gray	B		0	
	Dorsal raphe	B		0	
	Oculomotor nucleus	B		0	
Pons	Locus ceruleus	B		0	
	Median raphe	B		0	
	Abducens nucleus	B		0	
	Facial nucleus	B		0	
	Nucleus raphe interpositus	B		0	
Medulla	Hypoglossal nucleus	B		0	
	Dorsal efferent nucleus, vagus	B		0	
	Nucleus solitary tract	B		0	
	Olive	B		0	
Spinal cord	Cervical anterior horn cells	B		Not identified	
	Cervical corticospinal tract	B		Not identified	
	Thoracic anterior horn cells	B		0	
	Thoracic intermediolateral cell column	B		0	
	Lumbar anterior horn cells	B		0	
	Sacral nucleus of Onuf	B		0	
	Sacral anterior horn cells	B		0	

Arteriolosclerosis (H & E)

Arteriolosclerosis was assesed on H & E stained sections of anterior cingulate cortex, middle frontal gyrus, inferior frontal gyrus (pars opercularis), ventral striatum, middle insula, claustrum, putamen, globus pallidus, thalamus and angular gyrus.

Findings: Severe arteriolosclerosis was found in ventral striatum. Moderate arteriolosclerosis was found in thalamus.Mild arteriolosclerosis was found in anterior cingulate cortex, inferior frontal gyrus (pars opercularis), claustrum, putamen and angular gyrus. No arteriolosclerosis was found in other regions examined.

Microinfarcts (H & E)

White matter microinfarction was assessed on H & E stained sections of anterior cingulate cortex, middle frontal gyrus, inferior frontal gyrus (pars opercularis), ventral striatum, middle insula, claustrum, putamen, globus pallidus, thalamus and angular gyrus.

Findings: No microinfarctions were found in any region examined.

Lewy bodies (H & E)

H & E stained sections were reviewed for the presence of Lewy bodies. Regions reviewed included substantia nigra, locus ceruleus, dorsal motor nucleus of the vagus and amygdala.

Findings: No Lewy body pathology was found in any region examined.

Other significant pathology (H & E)

Findings: Severe pallor of thoracic, lumbar and sacral lateral corticospinal tracts

Aβ immunohistochemistry

Immunostaining for a-beta was used to detect neuritic and diffuse plaques, as well as cerebral amyloid angiopathy. Regions examined included cerebellar folia, dentate nucleus, substantia nigra, tectum, periaqueductal gray, dorsal raphe, oculomotor nucleus, anterior cingulate cortex, middle frontal gyrus, inferior temporal gyrus, middle insula, claustrum, putamen, globus pallidus, dentate gyrus, CA3-4, CA2, CA1/subiculum, entorhinal cortex, superior/middle temporal gyrus, angular gyrus and striate cortex.

Findings:

Neuritic Plaques: No neuritic plaques were found in any region examined.

Diffuse Plaques: Sparse diffuse plaques were found in middle frontal gyrus, superior/middle temporal gyrus and striate cortex. No diffuse plaques were found in other regions examined.

Amyloid Angiopathy: No cerebral amyloid angiopathy was found in any region examined.

Tau immunohistochemistry

Immunostaining for hyperphosphorylated tau (CP-13 antibody) was used to detect neurofibrillary tangles, globose tangles, Pick bodies, other neuronal cytoplasmic inclusions (NCIs, other than NFTs or Pick bodies), astrocytic plaques, tufted and thorny astrocytes, white and gray matter thread and grain pathology, and glial cytoplasmic inclusions (GCIs) other than those described above. Regions examined included substantia nigra, tectum, periaqueductal gray, dorsal raphe, oculomotor nucleus, locus ceruleus, median raphe, pontine nuclei, anterior cingulate cortex, middle frontal gyrus, ventral striatum, inferior temporal gyrus, middle insula, claustrum, putamen, globus pallidus, dentate gyrus, CA3-4, CA2, CA1/subiculum, entorhinal cortex, superior/middle temporal gyrus, precentral gyrus, postcentral gyrus, angular gyrus, posterior cingulate cortex and striate cortex.

Findings:

Neurofibrillary tangles: No NFT pathology was found in any region examined.

Globose tangles: No globose tangles were found in any region examined.

Pick Bodies: No Pick bodies were found in any region examined.

Neuronal cytoplasmic inclusions: No NCIs were found in any region examined.

Astrocytic plaques: No astrocytic plaques were found in any region examined.

Tufted astrocytes: No tufted astrocytes were found in any region examined.

Thorny astrocytes: No thorny astrocytes were found in any region examined.

Neuropil threads/grains: Moderate neuropil thread pathology was found in locus ceruleus. Mild neuropil thread pathology was found in dorsal raphe. No neuropil thread pathology was found in other regions examined.

White matter threads: No white matter thread pathology was found in any region examined.

Glial cytoplasmic inclusions: No GCIs were found in any region examined.

TDP-43 immunohistochemistry

TDP-43 immunohistochemistry was used to detect NCIs, neuronal nuclear inclusions, dystrophic neurites, dots, threads, and GCIs that represent pathological hallmarks of FTLD-TDP. Associated TDP-43 pathology may also be detected in the context of other primary pathological diagnoses. Regions examined included substantia nigra, tectum, periaqueductal gray, dorsal raphe, oculomotor nucleus, hypoglossal nucleus, dorsal motor nucleus of the vagus, nucleus of the solitary tract, inferior olive, anterior horn cells of lumbar spinal cord, intermediolateral column of thoracic spinal cord, anterior horn cells of thoracic spinal cord, anterior horn cells of sacral spinal cord, sacral nucleus of Onuf, anterior cingulate cortex, ventral striatum, inferior temporal gyrus, amygdala, dentate gyrus, CA3-4, CA2, CA1/subiculum, entorhinal cortex, superior/middle temporal gyrus, precentral gyrus, postcentral gyrus, angular gyrus and striate cortex.

Findings:

Neuronal cytoplasmic inclusions: Large numbers of NCIs were found in ventral striatum. Moderate numbers of NCIs were found in amygdala and dentate gyrus. Small numbers of NCIs were found in anterior horn cells of sacral spinal cord, anterior cingulate cortex, inferior temporal gyrus, CA1/subiculum, entorhinal cortex and postcentral gyrus. No NCIs were found in other regions examined.

Neuronal nuclear inclusions: No neuronal nuclear inclusions were found in any region examined.

Glial cytoplasmic inclusions: Small numbers of GCIs were found in anterior cingulate cortex, ventral striatum, entorhinal cortex, superior/middle temporal gyrus, precentral gyrus, postcentral gyrus and angular gyrus. No GCIs were found in other regions examined.

Dystrophic neurites: Large numbers of dystrophic neurites were found in anterior cingulate cortex, precentral gyrus, postcentral gyrus and angular gyrus. Moderate numbers of dystrophic neurites were found in anterior horn cells of sacral spinal cord, entorhinal cortex and superior/middle temporal gyrus. Small numbers of dystrophic neurites were found in substantia nigra, inferior olive, anterior horn cells of lumbar spinal cord, anterior horn cells of thoracic spinal cord, ventral striatum, inferior temporal gyrus, amygdala, dentate gyrus, CA1/subiculum and striate cortex. No dystrophic neurites were found in other regions examined.

Gray matter dots/threads: Large numbers of gray matter dots and threads were found in ventral striatum. Small numbers of gray matter dots and threads were found in anterior cingulate cortex, inferior temporal gyrus, amygdala and entorhinal cortex. No gray matter dots or threads were found in other regions examined.

White matter dots/threads: Small numbers of white matter dots and threads were found in anterior cingulate cortex. No white matter dots or threads were found in other regions examined.

α-synuclein immunohistochemistry

Alpha synuclein immunohistochemistry was used to detect Lewy bodies, Lewy neurites, and glial cytoplasmic inclusions. Regions examined included substantia nigra, tectum, periaqueductal gray, dorsal raphe, oculomotor nucleus, locus ceruleus, median raphe, pontine nuclei, hypoglossal nucleus, dorsal motor nucleus of the vagus, nucleus of the solitary tract, inferior olive, anterior cingulate cortex, middle frontal gyrus and amygdala.

Findings:

Lewy bodies:	No Lewy bodies were found in any region examined.
Lewy neurites:	No Lewy neurites were found in any region examined.
Glial cytoplasmic inclusions:	No glial cytoplasmic inclusions were found in any region examined.

Luxol Fast Blue (LFB)

Luxol Fast Blue/Periodic Acid Schiff stain was used to assess for long tract degeneration. Regions examined included cerebral peduncles, pyramids, and the lateral and anterior corticospinal tracts of the thoracic, lumbar, and sacral cord.

Findings: There is severe, focal pallor of the corticospinal tracts bilaterally at the levels of the pyramids and thoracic, lumbar, and sacral spinal cord. The lateral corticospinal tract is more significantly affected than the anterior corticospinal tract.

Interpretation:

This 65-year-old woman's illness began at age 49, with first symptoms relating to emotional distance from family, irritability, and anxiety, progressing to profound semantic deficits with striking preservation of visuospatial skills. The clinical syndromic diagnosis was the right temporal variant of semantic dementia (now referred to as semantic variant primary progressive aphasia), thought most likely due to underlying frontotemporal lobar degeneration (FTLD) pathology. The pattern of regional injury reflects the clinical features, with most severe degenerative changes involving the anterior temporal lobe, paralimbic belt, ventral striatum, and the upper motor neurons. Immunohistochemical analysis showed unequivocal evidence of FTLD-TDP, Type C, with frequent dystrophic neuritic inclusions in most regions examined, especially those implicated by the clinical syndrome. In addition, this case showed prominent degeneration of the corticospinal tracts in the absence of significant lower motor neuron involvement, justifying an additional designation of primary lateral sclerosis to indicate the extension of the TDP-43 proteinopathy into the pyramidal motor system as previously described in rare, long-surviving patients with FTLD-TDP, Type C[3]. Finally, there were two incidentally noted co-morbid pathologies: (1) mild arteriolosclerosis and (2) a low burden of Alzheimer's disease neuropathological change. These co-morbid pathologies are thought to have contributed little, if at all, to the patient's clinical deficits.

[redacted]

Associate Professor of Neurology

[redacted]

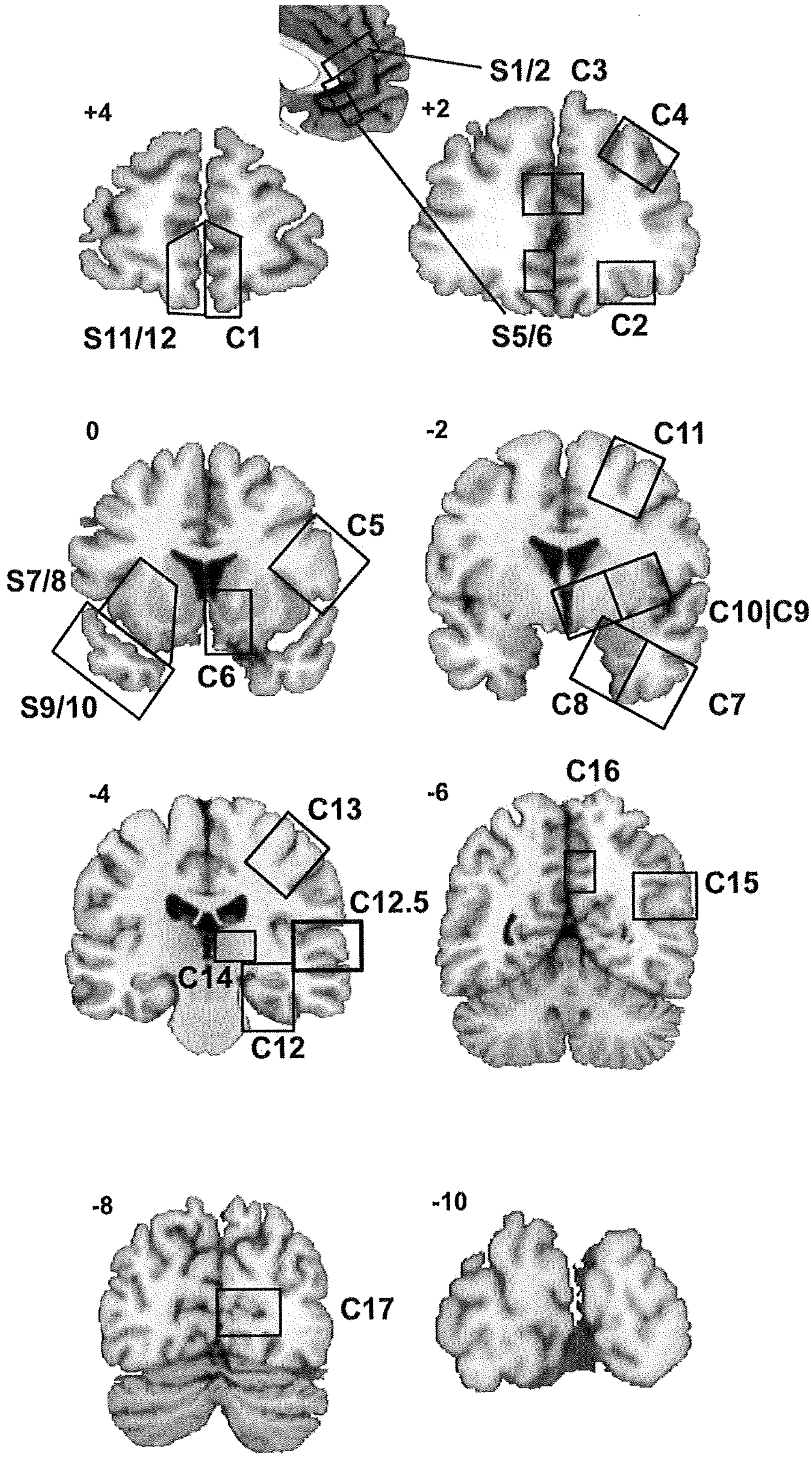
Professor of Pathology

References:

1. Mackenzie IR, Neumann M, Baborie A, et al. A harmonized classification system for FTLD-TDP pathology. Acta Neuropathol 2011;122:111-113.
2. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol 2012;123:1-11.
3. Josephs KA, Whitwell JL, Murray ME, et al. Corticospinal tract degeneration associated with TDP-43 type C pathology and semantic dementia. Brain : a journal of neurology 2013;136:455-470.

The information contained in this report was generated for the purpose of supporting research on neurodegenerative diseases. This report is not part of the permanent medical record and is not intended to guide medical decision-making.

UCSF ADRC Regional Sampling Scheme



Blocks taken:

Diagnostic

Slab +4 or +2 (circle)

C1. Frontal pole, medial (ant)

Slab +2

C2. Anterior orbital gyrus
C3. aMCC
C4. Middle frontal gyr

Slab 0

C5. Inferior frontal gyr, oper
C6. Ventral striatum

Slab -2

C7. Inferior temporal gyr
C8. Amygdala
C9. Insula/Putamen
C10. Globus Pallidus
C11. Superior frontal sulcus

Slab -4

C12. Hippocampus/ERC
C12.5 Superior temporal gyrus (post)
C13. Sensorimotor ctx (upper limb)
C14. Thalamus

Slab -6

C15. Angular gyrus
C16. PCC

Slab -8 or -10 (circle)

C17. Calcarine ctx

Brainstem

C18. Cerebellum/dentate nuc
C19. Midbrain (SN)
C19.5 Caudal midbrain
C20. Rostral pons (LC)
C21. Caudal pons (VIth
C21.5 Rostral medulla
C22. Medulla/olive (XII)

Spinal cord

C23. CX, TX, LX, SX

Research

Slab +4 or +2 (circle)

S11/12: Frontal pole, medial (post)

Slab +2

S1/2: pACC
S5/6: sACC

Slab 0

S7/8: FI
S9/10: Temp pole